The Final C7 Workshop

(Cerebellar-Cortical Control:

Cells, Circuits, Computation and Clinic)

Ma'ale Hachamisha hotel, Israel

May 5-8, 2013

http://www.bgu.ac.il/cmcw

Final C7 workshop
May 5-8, 2013
Ma'ale Hachamisha Hotel

European commission, Seventh Framework Program, Marie Curie Actions

Program:

Saturday, May4

Arrival to Ma'ale Hachamisha hotel
18:30 – 20:00 Dining hall open
22:00 Check in

Sunday, May 5

Session 1

- ☐ 9:00 - 9:30 **Suman Das**, Donchin lab
- ☐ 9:30 - 10:00 **Peter Holland**, Donchin lab
- ☐ 10:00 - 10:45 **Dana Cohen**, Bar-Ilan University
- ☐ 10:45 - 11:30 Coffee break

Session 2

- ☐ 11:30 - 12:00 **Aleksandra Smilgin**, Thier lab
- ☐ 12:00 - 12:30 **Zong-Peng Sun**, Thier lab
- ☐ 12:30 - 13:15 **Reza Shadmehr**, Johns Hopkins University
- ☐ 13:15 - 15:15 Lunch and poster session

Session 3

- ☐ 15:15 - 15:45 **Tafadzwa Sibindi**, Frens lab
- ☐ 15:45 - 16:15 **Eric Avila**, Frens lab
- ☐ 16:15 - 17:00 **Javier Medina**, University of Pennsylvania
- ☐ 17:00 Coffee break

Monday, May 6

Session 4

- ☐ 9:00 - 9:30 **Nicolas Gutierrez**, DeZeeuw lab
- ☐ 9:30 - 10:00 **Pascal Warnaar**, De Schutter lab
- ☐ 10:00 - 10:45 **Yosi Yarom**, Hebrew University
- ☐ 10:45 - 11:30 Coffee break

Session 5

- ☐ 11:30 - 12:00 **Christian Wilms**, Hausser lab
- ☐ 12:00 - 12:30 **Joao Couto**, De Schutter lab
- ☐ 12:30 - 13:15 **Vlastik Bracha**, Iowa State University
- ☐ 13:15 - 15:15 Lunch and poster session

Session 6

- ☐ 15:15 - 16:00 **Chris De Zeeuw**, Netherlands Institute for Neuroscience
- ☐ 16:00 - 17:00 PI meeting / Student meeting (beer!)

Tuesday, May 7

Session 7

- ☐ 9:00 - 9:30 **Maria Roxana Stefanescu**, Timmann lab
- ☐ 9:30 - 10:00 **Roxana Gabriela Burciu**, Timmann lab
- ☐ 10:00 - 10:45 **Tim Ebner**, University of Minnesota
- ☐ 10:45 - 11:30 Coffee break

Session 8

- ☐ 11:30-12:00 **Sebastien-Johannes Telgen**, Diedrichsen lab
- ☐ 12:00-12:30 **Katja Kornysheva**, Diedrichsen lab
- ☐ 12:30 - 13:15 **Fahad Sultan**, Berkeley
- ☐ 13:15-15:15 Lunch and poster session

Session 9

- ☐ 15:15 - 15:45 **Elise Lesage**, Miall lab
- ☐ 15:45 - 16:15 **Maria Dagioglou**, Miall lab
- ☐ 16:15 – 17:00 **Rich Ivry**, Berkeley
- ☐ 17:00 Coffee break
- ☐ 20:00 Festive dinner/ Final party

Wednesday, May 8

- ☐ 9:00 - 18:00 Hike / tour
- ☐ 18:00 - 21:00 Festive opening of CMCW

Thursday, May 9

- ☐ 9:00-18:00 CMCW

***"Between* the Mountains of Jerusalem *to* the Judean Lowland"**

'A hike through the biblical landscapes where ancient heroes have marched toward their eternal glory'

08:30 - we will leave the hotel after breakfast.

09:30 - The beautiful Tel Azekah (Azekah Mound), which is located at the upper reaches of the Valley of Elah, the top of Tel Azekah describes the mythical battle which took place nearby between **David and Goliath.**

12:30 - On our way we will have a picnic with our packed lunch and our traditional tea & coffee.

15:30 - We will reach Midras Ruins of a settlement which was active between the Iron Age (1,000 BCE) and the late Roman period; Midras Served as a guerrilla base, during the second Jewish revolt named after its great Judean leader **'Bar-Kokhba'**. The trail in Midras reveals the hiding tunnels and the caves- some of which is done by crawling and with the use of flashlights.

17:30 - Wine tasting in Hans Sternbach winery.

18:30 - The Festive Dinner in will take place in The Hans Sternbach Winery.

http://www.restaurants-in-israel.co.il/showartical.aspx?id=299

Bring with you: hats, long comfortable clothes (for crawling in the tunnels) and shows for a warm day, **flashlights**, camera, and sun's cream, in additional pare of clothes for the dinner.

* On this day we plan to hike for the most of the day.

All the best!

Looking forward to see you all!

Eitan- your guide on the trip.

You are more than welcome to contact me at – elninio76@gmail.com

Sunday Talks

Sunday, May 5

Session 1

- ☐ 9:00 - 9:30 **Suman Das,** "Unraveling the mechanistic pathway of trans-cranial direct current stimulation (tDCS) in cerebellar dependent adaptation learning"
- ☐ 9:30 - 10:00 **Peter Holland**, TBD
- ☐ 10:00 - 10:45 **Dana Cohen, "** Precision and synchrony in the olivo-cerebellum-nuceli loop"
- ☐ 10:45 - 11:30 Coffee break

Session 2

- ☐ 11:30 - 12:00 **Aleksandra Smilgin,** " Purkinje cells of the monkey oculomotor vermis respond to saccades as well as to smooth pursuit initiation"
- ☐ 12:00 - 12:30 **Zong-Peng Sun**, " Attempts to identify the role of caudal fastigial neurons in the control of saccadic eye movements"
- ☐ 12:30 - 13:15 **Reza Shadmehr**, "Sensitivity to error in the cerebellum"
- ☐ 13:15 - 15:15 Lunch and poster session

Session 3

- ☐ 15:15 - 15:45 **Tafadzwa Sibindi**, "Characterizing the effects of sum of sine stimuli on the linearity and non- linearities of the compensatory eye movement system"
- ☐ 15:45 - 16:15 **Eric Avila**, " Comparing non-human primate vermal and lateral cerebellar saccade related activity while performing a pro- and antisaccade task"
- ☐ 16:15 - 17:00 **Javier Medina**, "A calcium-based code for graded instructive signals in Purkinje cell dendrites"
- ☐ 17:00 Coffee break

Unraveling the mechanistic pathway of trans-cranial direct current stimulation (tDCS) in cerebellar dependent adaptation learning.

Suman Das[1, 2], Maarten A Frens [2], Chris de Zeeuw[2], Opher Donchin[1, 2]

[1]*Department of Bio-medical Engineering, BGU, Beer Sheva, Israel*

[2]*Department of Neuroscience, Erasmus MC, Rotterdam, The Netherlands*

The aim of this study is to explore the modulatory role of tDCS on cerebellar motor learning. tDCS is a noninvasive brain stimulation technique, used in a wide range of neurological and psychiatric disorders. Studies have confirmed the sub-threshold modulatory effects of tDCS on neuronal network (facilitation or inhibition). tDCS also boosts long-term plasticity mediated by brain-derived neurotropic factor (BDNF). Surprisingly, mechanism of tDCS on cerebellar motor learning remains unexplored. Therefore, my goals are - i) to find polarity specific dose-response curve of tDCS on cerebellar learning and (ii) to explore the pathways modulated by tDCS during cerebellar learning using mutant mice. I am using gain-down vestibulo-ocular reflex (VOR) behavioral paradigm to probe efficacy of tDCS. The VOR is a reflexive eye movement that functions to stabilize images on the retina by generating eye movements opposite to the direction of head motion. In gain down adaptation learning, the amplitude of the eye movement reduces compared to head movement. My preliminary results show that the effect of tDCS on cerebellar learning is dependent on its polarity as well as stimulus intensity. Anodal stimulation group learns faster than cathodal or sham group. Additionally, polarity specific effect of tDCS disappears when the intensity is lowered to a certain value. My next step is to find the effective range of tDCS on VOR learning. At the same time, I plan to use LTD deficient mutant mice in order to understand how tDCS modulates learning. By combining these two studies I will be able to show i) functional range of tDCS and (ii) how tDCS can modulate alternate pathways in LTD dependent cerebellar learning.

Peter Holland

TBD

Precision and synchrony in the olivo-cerebellum-nuceli loop.

Dana Cohen

The Gonda Brain Research Center, Bar Ilan University

The cerebellar nuclei which provide the sole output of the cerebellum are considered reliable relay stations capable of faithfully conveying synchronous activity in Purkinje cells. We tested this hypothesis by chronically recording and analyzing cerebellar nuclei activity in freely moving control and harmaline treated animals. In control animals our data reveal transient epochs of rhythmic activity at 7-8 Hz that occurred despite the lack of Purkinje cell rhythmicity reported under similar conditions. Oscillation epochs in different neurons exhibited a similar dominant frequency, high probability to co-occur and high coherence. In harmaline treated animals, the number of oscillating neurons substantially increased; however, in spite of the previously observed synchronized rhythmicity in Purkinje cells, nuclei oscillations were impaired. The oscillation dominant frequency was broadly distributed, bursts encoding the oscillations were inaccurate compared to control, the probability of two neurons to co-oscillate was similar to a random process and the coherence during co-oscillation epochs was substantially reduced. We suggest that these alterations and not the neuronal rhythmicity *per-se*, underlie the harmaline-induced body tremor. Our data provide evidence that disconfirm the role of the cerebellar nuclei as a relay station. We propose an alternative view in which within their dynamic range cerebellar nuclei neurons may extract and amplify concealed synchronized Purkinje cell ensemble activity while disregarding the stochastic background. When driven outside their dynamic range, for example by harmaline, the accurate spatiotemporal transformation is damaged yielding body tremor.

Purkinje cells of the monkey oculomotor vermis respond to saccades as well as to smooth pursuit initiation.

A. Smilgin, P.W. Dicke, P. Thier

Saccades and smooth pursuit eye movements (SPEM) are two types of goal directed eye movements whose kinematics differ profoundly, a fact that may have contributed to the notion that the underlying neuronal substrates may be separated to a large extent. By the same token, early work on the oculomotor role of the cerebellum seemed to suggest that also this part of the brain might dedicate distinct modules to the two types of goal directed movements, namely the flocculus/ parafloccculus to SPEM and the oculomotor vermis (OMV) to saccades. Yet, it became clear very soon that lesions of the OMV not only impair saccades but also the initiation of SPEM and that one may find saccade as well as SPEM related Purkinje Cell simple spikes (PC SS) responses in the OMV. Moreover, the early work by Suzuki and Keller (J. Neurophysiol. 1988 Jan;59(1):19-40.) seemed to indicate that at least some PCs are sensitive to both saccades and SPEM, a puzzling finding in view of the very different kinematic demands of the two. Such 'dual' OMV PCs might be oddities with little if any functional relevance. On the other hand, they might be representatives of an important computational principle serving as common ground for saccades and SPEM, deployed by the OMV.

With these considerations in mind, we set out to compare the preferences of eye movement related PC SS units recorded from the OMV for saccades and SPEM. 84 eye related SS units exhibited significant responses to both saccades and SPEM initiation. In accordance with previous observations, individual PCs responses showed highly idiosyncratic patterns (e.g. eye movement related bursts, pauses, burst-pause sequences etc.). We have previously demonstrated that even the responses of individual SPEM related PCs allow a reasonable description of SPEM initiation with eye velocity being the major kinematic variable reflected in the discharge (Dash et al., Cereb. Cortex 2012 Apr;22(4):877-91.). In order to figure out if the same holds for saccades, we fitted the responses of individual PCs with a linear model with eye position, velocity and acceleration as independent variables. Independent of the type of eye movement, eye position and velocity were able to explain a substantial amount of the discharge variance. Yet, eye velocity sensitivity was substantially higher for SPEM, thereby compensating for the much lower eye velocities. This finding suggests that OMV PC SS might deploy signals primarily used to optimize eye movements in the face of viscous forces.

Acknowledgement: This work was supported by the European commission; Marie Curie Initial Training Network, contract number PITN-GA-2009-238214

Attempts to identify the role of caudal fastigial neurons in the control of saccadic eye movements.

Zong-Peng Sun, Marc Junker, Peter W. Dicke, Peter Their

Department of Cognitive Neurology, Hertie Institute for Clinical Brain Research, University of Tübingen

We have previously shown that the discharge of Purkinje cell (PC) simple spikes in the oculomotor vermis (OV), comprising vermal lobules VI and VII, adjusts the size of a saccade by controlling its duration (Prsa & Thier 2011). The caudal fastigial nucleus (cFN) is the major target of saccade-related PC axons from the OV. Previous work on cFN saccade-related neurons seems to be in general in line with the notion that the cerebellum controls the timing of saccades. cFN neurons burst early for saccades in the contraversive direction, and burst later for saccades in the ipsiversive direction (Ohtsuka & Noda 1991), a pattern that has been taken to suggest a relationship to saccade start and end respectively. Moreover, adaption changes the time of the ipsiversive burst (Scudder & McGee 2003). A weakness of previous work on the cFN has been the small number of neurons studied as well as the assumption that the cFN consists of a functionally homogenous population of neurons. However, this assumption is hardly justified in view the fact that the cFN - like any other part of the deep cerebellar nuclei (DCN) - contains distinct types of neurons, interneurons as well as projection neurons with the latter contacting a number of different brainstem targets such as excitatory and inhibitory saccade related burst neurons in the paramedian pontine reticular formation (PPRF), omnipause neurons in the reticular formation, the more rostral regions of the superior colliculus as well the inferior olive (May et al 1990). In an attempt to find evidence for functionally distinct types of cFN neuron we have been carrying out single-unit recordings from the DCN of 2 rhesus monkeys. Based on MRI guided stereotaxis and physiological landmarks, the assignment of units to the cFN is tentative, as histological reconstruction of recording sites is not available yet.

A total of 160 neurons encountered in the DCN have been recorded so far. Of these, 46 eye-movement related units responded to visually guided saccades studied. Only 24 in this latter group showed the typical saccade related bursts emphasized by previous work. The others exhibited more complex patterns such as pauses or tonic responses. The 8 out of 24 units that could be studied during gain-decrease (=inward) adaptation, running a standard McLaughlin paradigm, exhibited varying changes in the number of spikes fired around the saccade. Importantly, none showed clear changes of their timing. So far our attempts to parse the small sample of saccade-related neurons into functionally distinct clusters based on differences in spike wave-form and firing statistics have remained unsuccessful. We are currently trying to increase the sample size and to obtain additional information on the location of saccade related unit by microstimulation.

References:

May PJ, Hartwich-Young R, Nelson J, Sparks DL, Porter JD. 1990. Cerebellotectal pathways in the macaque: implications for collicular generation of saccades. *Neuroscience* 36:305-24

Ohtsuka K, Noda H. 1991. Saccadic burst neurons in the oculomotor region of the fastigial nucleus of macaque monkeys. *J Neurophysiol* 65:1422-34

Prsa M, Thier P. 2011. The role of the cerebellum in saccadic adaptation as a window into neural mechanisms of motor learning. *Eur J Neurosci* 33:2114-28

Scudder CA, McGee DM. 2003. Adaptive modification of saccade size produces correlated changes in the discharges of fastigial nucleus neurons. *J Neurophysiol* 90:1011-26

Sensitivity to error in the cerebellum.

Reza Shadmehr

Johns Hopkins School of Medicine

For over 40 years, the main hypothesis regarding the function of complex spikes (CS) in the cerebellum has been that they encode errors. The basic prediction of this error hypothesis is that there should be a positive correlation between probability of CS and error magnitude. Recently, neurophysiological experiments have recorded CSs during motor adaptation and have observed that as errors decline with training, probability of CS does not decline. Furthermore, as errors increase in 'random perturbation' paradigms in which the mean error over a training block is zero, probability of CS decreases.

Therefore, experimental data is strongly inconsistent with the idea that CS encodes an error signal. What is encoded by complex spikes?

We suggest that in principle, learning from trial-to-trial should not only depend on prediction error, but also a measure of sensitivity to that error. We show that in humans, this sensitivity is greatest for small errors, and can be modulated by four folds depending on task statistics. We then show that in monkeys, probability of CS in the oculomotor vermis is also largest for small errors, and that for a given error magnitude, this probability is higher when the animal shows greater learning from error. Putting the human and monkey data together, we propose that complex spikes do not encode error, but rather encode sensitivity to error, which in turn guides learning in the Purkinje cells.

Characterizing the effects of sum of sine stimuli on the linearity and non-linearities of the compensatory eye movement system.

T. M. Sibindi[1], M. Ginzburg[2], O. Donchin[1,2], M. A. Frens[1]

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Compensatory eye movements (CEM) maintain a stable image on the retina using visual and vestibular input to drive eye movements that cancel movements of the head and surroundings, thereby preventing retinal slip. The optokinetic reflex (OKR) and the vestibular ocular reflex (VOR) compensate for low and high velocity stimuli, respectively. The VOR system is considered and modelled as a linear system and should satisfy the superposition and homogeneity principles. The OKR system is known to be highly non-linear. We recorded eye movements in response to sinusoidal stimulation to test whether any combination of applied stimuli would output eye movements that satisfy the superposition principle. We tested the linearity of the VOR and OKR systems using non-harmonic Sum of Sine stimuli (SoS) and single sine (SS) in C57Bl6 mice. We collected behavioural data in four CEM conditions: VOR, OKR, visually-enhanced VOR and suppressed VOR. SoS combinations used were 0.6/0.8hz; 0.6/1.0hz; 0.8/1.0hz; 1.0/1.9hz with each frequency at 1 or 2 degrees. We compared the gains/phases of SS stimuli with SoS stimuli. Suppression of gain was seen in the OKR during SoS and some gain enhancement was seen in VOR and SVOR conditions indicating non-linearities in the CEM system. The results are compatible with the notion of prediction signals during SS stimulation that enhances the behavioural response and thus increases the gain of the OKR. To further investigate the source of the non-linearities, we collected behavioural and electrophysiological data from the flocculus. Finally, the State Predicting Feedback Control (SPFC) model of Frens & Donchin (2009) was tested in the four CEM conditions and it reproduced accurately the gain/phase of the behavioural responses, the main properties of the CEM system and correctly predicted non-linearities in OKR responses. Combining SoS data with data of the SPFC model, we can begin to unravel the non-linearities of the CEM system.

Comparing non-human primate vermal and lateral cerebellar saccade related activity while performing a pro- and antisaccade task.

Eric Avila[1,2], Moshe Godschalk[2], Pieter Roelfsema[2], Chris van der Togt[2], Peter Holland[1], Peter Thier[3], Maarten A. Frens[1], Chris I. De Zeeuw[1,2]

[1] *Department of Neuroscience, Erasmus MC, Rotterdam, The Netherlands.*

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[3] *Department of Cognitive Neurology, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany.*

Anatomical and functional evidence suggests that the cerebellum processes motor and non-motor information as its inputs and outputs form part of a closed loop with cortical structures. At the time there is no consensus and experiments lack to show how the cerebellum might be processing cortical information as part of this loop. The cerebellum builds up internal models that manage motor activities that code for prediction of sensory consequences of movements. A correct prediction develops as a result of learning from a past experience. Given its highly similar topography throughout its regions, the same algorithm may be applied to all its inputs. Is this cerebellar output effecting motor commands only or is involved in more complex and abstract information processing such as decision-making (executive functions)? Our aim is to contribute our understanding of how the cerebellum may be participating in these complex cognitive processes. We used a pro- and antisaccade task that requires a monkey to suppress a reflex saccade to a shown target and direct its gaze to a mirror position. This type of inhibition is known to engage prefrontal regions (goal-oriented behavior). We trained two non-human primates (macaca mulatta) to perform interleaving pro and anti saccadic eye movements while recording saccade related activity in Purkinje cells in Lobules Vic and VII in vermis and lateral hemisphere (Crus I and II). We present preliminary results obtained of one non-human primate.

A calcium-based code for graded instructive signals in Purkinje cell dendrites.

Javier F Medina

University of Pennsylvania

Instructive signals play an essential role in the process of motor learning because ultimately, they are the ones in charge of triggering neural plasticity when an incorrect movement needs to be modified. In the first half of my talk, I will argue that to be useful, instructive signals should do more than simply sound the alarm if a movement is made incorrectly; they should also provide graded information about how much the movement should change. I will present data from a series of behavioral experiments of eyeblink conditioning in head-fixed mice, a cerebellar-dependent type of motor learning. The findings clearly demonstrate that the strength of the periocular airpuff stimulus, which is the instructive signal in this task, provides graded information that dictates how much the conditioned eyelid movement will be modified. To follow up on these findings, in the second half of my talk I will examine how the cerebellum encodes information related to the strength periocular airpuffs. For eyeblink conditioning, airpuff-related instructive signals are thought to be encoded by activation of the powerful climbing fiber input, which results in a large increase of calcium in the post-synaptic Purkinje cell that triggers a variety of plasticity mechanisms. I will present data from experiments in awake mice, using two-photon imaging to monitor Purkinje cell dendritic calcium signals in response to periocular airpuffs of different strengths. The findings suggest that graded information about airpuff strength is encoded by calcium signals both at the level of individual and the population of Purkinje cell dendrites.

Monday Talks

Monday, May 6

Session 4

- ☐ 9:00 - 9:30 **Nicolas Gutierrez**, "Size does not always matter: Ts65Dn Down syndrome mice show cerebellum- dependent motor learning deficits that cannot be rescued by SAG-treatment"
- ☐ 9:30 - 10:00 **Pascal Warnaar**, "How complex spikes look like"
- ☐ 10:00 - 10:45 **Yosi Yarom**, " The nuclear-olive control of coupling coefficient and oscillatory activity"
- ☐ 10:45 - 11:30 Coffee break

Session 5

- ☐ 11:30 - 12:00 **Christian Wilms**, " Protein distributions underlying differential dendritic calcium signaling in cerebellar Purkinje cells"
- ☐ 12:00 - 12:30 **Joao Couto**, "Frequency dependency of the Phase Response Curve in the Purkinje cell"
- ☐ 12:30 - 13:15 **Vlastik Bracha**, "Intermediate cerebellum and motor learning: the role of task-related signals and the dark energy of brain"
- ☐ 13:15 - 15:15 Lunch and poster session

Session 6

- ☐ 15:15 - 16:00 **Chris De Zeeuw**, "Creating Cerebellar Coordination through Distributed Cerebellar Plasticity"
- ☐ 16:00 - 17:00 PI meeting / Student meeting (beer!)

Size does not always matter: Ts65Dn Down syndrome mice show cerebellum-dependent motor learning deficits that cannot be rescued by SAG-treatment.

N. Gutierrez-Castellanos

Netherlands Institute for Neuroscience, Royal Netherlands Academy of Arts & Sciences, Amsterdam, The Netherlands

Individuals with Down syndrome (DS) and Ts65Dn mice both show a reduced volume of the cerebellum due to a significant reduction in the density of granule neurons. Recently, the cerebellar hypoplasia in Ts65Dn mice was rescued by a single treatment with an agonist of the sonic hedgehog pathway on the day of birth. In addition to normalizing cerebellar morphology, this treatment restored the ability to perform learning and memory tasks associated with the hippocampus. It is not clear to what extent improved spatial navigation result from improvement of the cerebellar architecture or to a yet undefined role of sonic hedgehog in peri-natal hippocampal development. The absence of a clearly demonstrated deficit in cerebellar function in trisomic mice exacerbates the problem of discerning how SAG acts to improve learning and memory. Here we show that phase reversal adaptation of the vestibulo-ocular reflex is significantly impaired in Ts65Dn mice, providing for the first time a precise and sensitive phenotype of cerebellar function. However, these deficits do not benefit from the normalization of morphology following treatment with SAG. The lack of improvement at this functional assay and synaptic properties of Purkinje cells by SAG treatment, supports the possibility of a direct effect of Shh pathway stimulation on the hippocampus explaining the benefits of this potential approach to the improvement of cognition in DS.

How complex spikes look like.

Pascal Warnaar

CSs in vivo show highly variable waveforms, both over different cells as in single cells. Difference is found in the CS lengths, the number of spikelets and their relative timing within the spike. An underlying cause of variability in the waveforms is coming from the IO derived trigger signal, potentiating the IO-PC pathway to send divergent information through the CS trigger signal. This study will show systematically the variability observed in the CS waveforms. Part of the variety seen comes from a CS interval related mechanism. Correlation of SS spike timing dynamics before CSs and the following waveforms was not observed, nor did CS waveforms suppress or facilitate spiking activity differentially.

The nuclear-olive control of coupling coefficient and oscillatory activity.

Y. Yarom

Hebrew University

The chemical inputs to olivary neurons, as well as the electrical connections between the neurons are morphologically organized in specific structure: the olivary glumerulus. In this structure dendritic spines of neighboring olivary neurons are connected via gap junction and surrounded by both excitatory and inhibitory synaptic terminals. The source of the inhibitory terminals was traced to the deep cerebellar nuclei where a subgroup of GABAergic neurons projects specifically to the inferior live. This special arrangement gave rise to the hypothesis that the strength of the electrical coupling between olivary neurons is modulated by synaptic input. The modulation of the coupling strength plays a major role in several cerebellar models, by either providing dynamic modulation of the level of synchrony between olivary neurons or generating the subthreshold voltage oscillation. Although this possibility was solely based on anatomical observations it is central to many models describing cerebellar function.

Using optogenetic techniques we succeeded in expressing channelrhodopsin (ChR2) specifically in the nuclear-olive (NO) projection cells. With this highly specific system we demonstrate, in an in-vitro system, that the inhibitory input from the NO projection cells is located mainly at dendritic sites and occasionally at the junction between dendrites. Light activation of this input efficiently reduces the coupling coefficient and totally blocks the subthreshold voltage oscillations.

Protein distributions underlying differential dendritic calcium signaling in cerebellar Purkinje cells.

Wilms C.D.[1], Branco T.[1], Micheva K.D.[2], Smith S.J.[2] & Hausser M.[1]

1) Wolfson Institute for Biomedical Research, UCL, London, UK
2) Dept. of Molecular and Cellular Physiology, Stanford University, Stanford, CA, USA

Cerebellar Purkinje cells (PC) receive on the order of 150,000 glutamatergic parallel fiber (PF) inputs onto their dendrites. Recent in vivo experiments have shown that sensory stimulation recruits PFs in bursts of 2 – 5 action potentials, and that recruited PFs are spatially clustered. It is not known how PC dendrites integrate this spatio-temporal activation pattern – both electrically and biochemically.

Here we describe how physiological spatio-temporal PF activation patterns are integrated by PC dendrites. We used patterned two-photon uncaging of MNI-glutamate in cerebellar slices, in combination with somatic whole-cell recording and two-photon calcium imaging. Based on results from in vivo measurements of PF and granule cell activity, we stimulated groups of 8 diffraction-limited spots within a radius of 10 µm, delivering two uncaging pulses per spot at 100 Hz. We found calcium transients resulting from activation of both voltage-gated calcium channels ("early") and metabotropic glutamate receptors ("delayed"). Individual branches reproducibly displayed very different combinations of these two components, even when belonging to the same parent dendrite. Surprisingly, dendritic calcium signals were not directly correlated with the corresponding electrical somatic response. Furthermore, the calcium response type did not correlate with morphological parameters (branchlet length, density of the stimulated spines within the branchlet, or distance of the stimulated spine group from the tip or base of the dendrite). These findings suggest that differential expression of voltage-gated channels and proteins involved in mGluR1 signal transduction might underlie the branch-specific calcium signaling we observe. We are now probing this mechanism by combining functional and proteomic microscopy: After response properties of dendritic branchlets were determined by glutamate uncaging, the relative density of calcium signaling molecules in these dendrites are probed using array tomography. Initial experiments indicate that at least two involved proteins (mGluR1 and P/Q-type channels) are differentially distributed.

Inter-branch variations in calcium signaling suggest that PC dendritic branches can individually regulate and compartmentalize their integrative properties. Our approach will allow identification of cellular mechanisms responsible for implementing this compartmentalization.

Frequency dependency of the Phase Response Curve in the Purkinje cell.

João Couto, Daniele Linaro, Professors Erik de Schutter and Michele Giugliano.

Theoretical Neurobiology Unit, the University of Antwerp

Understanding information processing in the cerebellum requires a detailed knowledge of how individual neurons process their synaptic inputs. In our study we focused on Purkinje cells (PCs), as they represent the output stage of the cerebellar cortex and possess unique morphology and functional connectivity. In addition, as opposed to other cell types in the brain, PCs fire spontaneously in the absence of synaptic input. This makes the study of their intrinsic biophysical properties a first essential step, towards dissecting cerebellar microcircuits computations.

A method that received increasing consensus for expressing concisely the input-output response properties of a PC is the experimental characterization of its phase response curve (PRC). This is a way to express how the cell responds to an incoming brief external perturbation, depending on its occurrence time with respect to PC oscillation cycle. By this method, an earlier pioneering study intriguingly suggested that PCs firing at low output rates behave as phase-independent integrators, while PCs firing at higher output rates, as phase-dependent integrators.

While this result raised great interest for its computational consequences, it left unanswered the question on whether PCs integration properties transition abruptly or smoothly from one mode to the other. We find that the transition is not abrupt but rather progressive and smooth. In our study, we employed whole-cell recordings from the somata of Purkinje cells in acute cerebellar tissue slices, and investigated further this phenomenon. Amending the standard experimental protocol, we developed a new closed-loop approach to more efficiently probe the PRC at a desired spiking frequency. This allowed us to obtain an extensive characterization of the PRCs over a wide range of frequencies for the same cells, in over 40 neurons. As it was unexplored in the early report, we found that different stimulation amplitudes shape the signal-to-noise ratios in PRC estimation. By indirect estimation methods, we also show the PRC spike-frequency dependence is not an artefact of the method employed.

Our observations confirm that while at low firing rates PCs are less sensitive to the precise timing at which inputs arrive, at high frequencies PCs preferentially respond to incoming inputs occurring during late oscillation phases. By providing this thorough description of the PRCs frequency dependency in PCs, we offer the theoretical community a more solid experimental picture, grounding the study of PCs synchrony emergence and of how cerebellar information processing depends on precise spike times.

Intermediate cerebellum and motor learning: the role of task-related signals and the dark energy of brain.

Vlastislav Bracha

Iowa State University, Ames, Iowa, USA

The intermediate cerebellar cortex and interposed nuclei control classically conditioned eyeblinks. Results of studies utilizing the eyeblink conditioning model constitute one of the pillars for contemporary notions of cerebellar involvement in motor learning. Besides this function, inactivation studies suggest that the mammalian intermediate cerebellum controls variety of other reflexive and voluntary movements. Examples of these movements are limb withdrawal reflexes, limb tactile and visual placing reflexes, reaching and grasping movements and instrumentally conditioned eyelid movements. The mechanisms by which the cerebellum contributes to these behaviors are poorly understood. Resolving the intermediate cerebellar role in movement control and learning requires determining specific roles of cerebellar tonic and phasic, task-related signals. The problem is that these two variables have been difficult to dissociate. In this presentation, I will use our recent data to outline advantages and limitations of two promising approaches to this challenge – the combined application of neurotransmitter receptor agonists and antagonists and the optogenetic method.

Creating Cerebellar Coordination through Distributed Cerebellar Plasticity.

Chris I. De Zeeuw

Dept. of Neuroscience, Erasmus MC, Rotterdam; Netherlands Institute for Neuroscience, Royal Dutch Academy of Arts & Sciences, Amsterdam

Neurons in the brain communicate with each other in a digital fashion by evoking or silencing spike activities. Most theories about information processing in the cerebellum assume that increases and decreases of average spike activities form the main sources of information exchange that will ultimately induce changes in motor behavior. Recent electrophysiological recordings during motor coordination indicate that feedback from the inferior olive to the cerebellum dominates the phase of Purkinje cell activities and motor performance and that cerebellar interneurons are required for the precise temporal patterns of these activities and consolidation of learned motor behavior. Disturbances in these patterns, either by forcing the spikes to fire out of phase (rate coding) or to fire too regular or irregular (temporal coding), can lead to ataxia and/or serious problems in procedural memory formation. In this lecture I will illustrate how each cell type and form of plasticity in the cerebellar network is perfectly designed to contribute to specific rate codes and temporal patterns of spike activities, how these codes and patterns might contribute to phase control and consolidation of procedural memory formation, which factors can disturb these codes and patterns, and how these disturbances can lead to neurological diseases.

Tuesday Talks

Tuesday, May 7

Session 7

- ☐ 9:00 - 9:30 **Maria Roxana Stefanescu**, "A comparative study of cerebellar activation in SCA3, SCA6 and Friedreich's ataxia using 7T fMRI"
- ☐ 9:30-10:00 **Roxana Gabriela Burciu** " Recovery of motor function in cerebellar disease"
- ☐ 10:00 - 10:45 **Tim Ebner** " In vivo Optical Imaging of Circuitry Changes in Mouse Models of Cerebellar Disease "
- ☐ 10:45 - 11:30 Coffee break

Session 8

- ☐ 11:30-12:00 **Sebastian-Johannes Telgen**, " Building versus recalibrating internal models for motor control"
- ☐ 12:00-12:30 **Katja Kornysheva**, " Cortical and cerebellar encoding of sequential movement parameters"
- ☐ 12:30-13:15 **Fahad Sultan**, " The evolution of the vertebrate and the hominoid brain from a cerebellar perspective"
- ☐ 13:15-15:15 Lunch and poster session

Session 9

- ☐ 15:15 - 15:45 **Elise Lesage,** "Language and the cerebellum"
- ☐ 15:45 - 16:15 **Maria Dagioglou,** "State Estimation in Tracking and Exploration"
- ☐ 16:15 – 17:00 **Rich Ivry**, " Interplay of strategies and adaptation in motor learning"
- ☐ 17:00 Coffee break
- ☐ 20:00 Festive dinner/ Final party

A comparative study of cerebellar activation in SCA3, SCA6 and Friedreich's ataxia using 7T fMRI.

Maria Roxana Stefanescu [1,2]

[1] *Department of Neurology, University of Duisburg-Essen, Germany;*
[2] *Erwin L. Hahn Institute for Magnetic Resonance Imaging, University of Duisburg-Essen, Germany;*

Spinocerebellar ataxia (SCA) type 3 and type 6 are autosomal dominant cerebellar ataxias. Friedreich's ataxia (FRDA) is an autosomal recessive disease. SCA3, SCA6 and FRDA are trinucleotide repeat disorders with different age of onset. Different parts of the cerebellum are affected. SCA6 is known by Purkinje cell loss. SCA3 and FRDA are associated with abnormalities of the dentate nuclei. We investigated whether or not different patterns of activations of the cerebellar cortex and nuclei can be observed using high-field functional magnetic resonance imaging (7T fMRI). Twelve FRDA patients, ten SCA3 patients and twelve SCA6 patients were tested and compared to gender- and age-matched controls. Participants performed opening and closing movements of the right fist. Movements were acoustically paced at 0.6 Hz and recorded using an MRI-compatible glove. Movement frequency was not significantly different between groups. The fMRI data were corrected for physiological artifacts (pulse, breathing). Both patients and controls showed activations within the known hand areas of the cerebellar cortex (lobules V, VI, and IV, and VIII) predominantly on the right. Activation was less in all patient groups compared to controls. Activation of the cortex was least in FRDA patients, followed by SCA3 and SCA6 patients. On the level of the dentate nuclei, controls activated predominantly dorsorostral parts bilaterally. In patients activation of the nuclei was generally less compared to controls. Again, activation of the dentate nuclei was least in FRDA patients, followed by SCA6 and SCA3. Whereas reduced activation of the cerebellar nuclei was expected in SCA3 and FRDA patients, reduced activation of the cerebellar cortex may be explained by reduced afferent input. In contrast, comparatively preserved activation of cerebellar cortex in SCA6 may be due to preserved mossy fiber input. Reduced Purkinje cell input may have caused reduced activation of the nuclei in SCA6.

Recovery of motor function in cerebellar disease.

Roxana Gabriela Burciu

Department of Neurology, University of Duisburg-Essen, Germany

Damage to the cerebellum leads to difficulties in performing coordinated voluntary movements, interfering with activities of daily life. Nonetheless, many patients exhibit a certain degree of recovery in the weeks, months, and sometimes even years following disease onset, which may be related to structural and functional changes of the remaining brain tissue. The present project sought to identify and better understand the mechanisms that underlie recovery of function in these patients using a range of behavioral and neuroimaging techniques. First, a longitudinal study of patients with cerebellar degeneration revealed that daily practice (for two weeks) of a postural task involving the displacement of the body's center of gravity resulted in significant, long-lasting improvement of motor function. Such training-related gains were supported by gray matter changes of primarily nonaffected regions of the cortico-cerebellar loop and to a lesser extent cerebellar hemispheres. Structural modifications in response to cerebellar disease are not the only changes the brain undergoes. In a second study we examined differences in patterns of brain activity at rest following acute (or chronic) stroke of the cerebellum/ resection of cerebellar tumors. Results pointed to an increased activation of various resting-state networks in the more acute stage of the disorder compared to the chronic one, where the pattern of brain activity closely resembled that of healthy individuals. Therefore, the integrity of brain networks could represent a measure of functional recovery after the occurrence of cerebellar lesions. Finally, in a third project, we showed that in patients with acute focal lesions of the cerebellum the degree of adaptation to externally imposed perturbations to the arm depends on the integrity of the more anterior cerebellar structures. Lesions of the inferior structures of the cerebellum were commonly not associated with impaired motor adaptation. Altogether, while a clear causal link between the brain's reorganization and functional recovery has yet to be established, present results suggest that plastic changes following cerebellar damage do occur and should be further explored with the ultimate goal of designing rehabilitation strategies.

In vivo Optical Imaging of Circuitry Changes in Mouse Models of Cerebellar Disease.

Timothy J. Ebner, Samuel W. Cramer, Justin A. Barnes, and Gang Chen

Department of Neuroscience, University of Minnesota

This talk will discuss how flavoprotein autofluorescence and Ca2+ optical imaging in the cerebellar cortex, in vivo, is being used to investigate dysfunction in the cerebellar circuitry in mouse models of cerebellar diseases. The flavoprotein signal is mitochondrial in origin and is due to the oxidation and reduction of flavoproteins during oxidative metabolism in neurons. Closely coupled to neuronal activity, the flavoprotein signal can be used to monitor in the cerebellar cortex neuronal excitation and inhibition, synaptic plasticity, and the functional architectures. Use of optical imaging to understand the cerebellar circuit dysfunction will be highlighted in three disease models. In transgenic mouse models of the polyglutamine-induced neurodegenerative disorder, spinocerebellar ataxia type 1 (SCA1), flavoprotein and Ca2+ imaging demonstrate a loss of climbing fiber activation of Purkinje cells in early symptomatic animals. Parallel fiber-Purkinje cell synaptic transmission is relatively normal until late in the disease. Furthermore, the abnormalities in CF-PC synaptic transmission were ameliorated when mutant transgene expression was prevented during postnatal cerebellar development, demonstrating the susceptibility of the climbing fiber-Purkinje circuit to the mutant protein and the importance of this circuit in the motor phenotype. Spinocerebellar ataxia type 5 (SCA5), a dominant neurodegenerative disease characterized by profound Purkinje cell loss, is caused by mutations in the SPTBN2, a gene which encodes β-III spectrin. In a recent mouse model created to understand the mechanistic basis for disease, the results show that endogenous β-III spectrin interacts with the metabotropic glutamate receptor 1α and that mice expressing mutant β-III spectrin have progressive cerebellar degeneration. In vivo optical imaging demonstrates decreased mGluR1-mediated responses and deficient mGluR1-mediated long-term potentiation. These results suggest mutant β-III spectrin prevents mGluR1α anchoring at specific cell membrane domains and link SCA5 to other disorders involving glutamatergic dysfunction and synaptic plasticity abnormalities. In the third example, optical imaging was used to investigate the changes in the cerebellar cortex in the tottering mouse, a model of episodic ataxia type 2. Both are channelopathies involving a mutation in the gene encoding P/Q-type voltage-gated Ca2+ channels. The tottering mouse phenotype includes dramatic, transient motor attacks of dystonia. Flavoprotein optical imaging revealed transient, low frequency oscillations in the cerebellar cortex of tottering mice. These highly abnormal oscillations are present in the Purkinje cell firing and disrupt cerebellar cortical function. In the awake tottering mouse, the low frequency oscillations are accentuated during the episodic dystonia and become coherent with oscillations in the limb muscles. The low frequency oscillations and associated cerebellar cortical dysfunction demonstrate a novel abnormality in the tottering mouse in which the cerebellar circuitry enters an aberrant excitability state that results in transient neurological dysfunction.

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Mechanisms of motor learning: Adaptation versus skill in reaching movements

Sebastian Telgen, Darius Parvin, Jörn Diedrichsen

Institute of Cognitive Neuroscience, University College London, UK

Cerebellar patients show severe deficits in adaption for a range of effectors and tasks, while other forms of motor learning, such as skill learning, are typically preserved. However it is not clear what sets adaptation and other types of motor learning apart.

Adaptation and skill learning are still predominantly differentiated by the type of task that is used to study them. We argue that the differentiation should be based on mechanisms rather than tasks: We define adaptation as a recalibration of an existing control policy, and skill learning as the establishment of a novel control policy that first needs longer planning and later can be recalled more efficiently. Our results show that it is possible to observe both mechanisms within a single reaching task, differing only in the type of visuo-motor transformation that is imposed.

Skill learning and adaptation were studied using a reaching task, where the visual feedback was either mirrored around the midline or rotated by 40 degrees. Participants performed reaching movements in two separate sessions. Between the first and the second session was a 12 or 24 hours delay.

In the mirror-reversal learning task we observed a strong relationship between RT and movement direction, with shorter RTs leading to movements into the wrong direction. This speed-accuracy trade-off progressively shifted during learning, such that the same movement accuracy was achieved at shorter RTs. We argue that this is the signature of a new control policy becoming automatized. We also directly observed an overlap of the old and new control policy within single trajectories by probing fast feedback responses to lateral displacements of the visual cursor. Even in the end of training, participants responded initially with a correction in the old direction, and only reversed their response later in the movement.

During visual-rotation there was no relationship between RT and movement direction, i.e. fast and slow trials showed similar movement error in all phases of learning. We interpret this as evidence for the recalibration of an existing and automatic control policy. Learning also differed in how behaviour changed in the break between the experimental sessions. For visual rotation, significant overnight forgetting was observed. For mirror-reversal, we found significant offline gains, i.e. improvements in the speed-accuracy trade-off in the feedforward and the feedback command.

Mirror reversal learning shares speed-accuracy trade-offs, automatization and offline gains with many other skill learning tasks. Therefore, our results demonstrate that visual rotation and mirror reversal learning are subserved by two different learning mechanisms. Further experiments will need to test the idea that the cerebellum is primarily involved in the recalibration of an existing, but not in the acquisition of a new control policy.

Cortical and cerebellar encoding of sequential movement parameters.

Kornysheva K, Diedrichsen J

The production of skilled sequences involves the control of both the ordering of individual movements, as well as their relative timing. Which neural representations underlie these components is currently not well understood. We used multivariate pattern analysis of fMRI data to reveal how ordinal and temporal representations are distributed across neocortical regions and the cerebellum. Over the course of three days, subjects acquired 9 different right hand finger sequences, which were unique combinations of 3 finger order (ordinal) and 3 timing (temporal) structures. Although these features were never trained in isolation, reaction time analysis revealed savings associated with the temporal and ordinal structures of the learned sequences, in accordance with our previous findings (Kornysheva et al. 2013). Multivariate classification analysis revealed an overall encoding of the 9 sequences in bilateral (pre-)motor and parietal regions, as well as in the ipsilateral lobule VI of the cerebellum. An integrated representation for ordinal and temporal structure could be found in the contralateral primary motor cortex only. Overlapping, but independent representations of timing and order could be observed in premotor motor areas bilaterally, with ordinal representations located in contralateral dorsal premotor and parietal areas and temporal representations primarily in ipsilateral ventral premotor areas. The (pre-)supplementary motor area revealed overall sequence encoding with stronger tuning for timing on the ipsilateral and for order on the contralateral side. Our study for the first time decomposes the encoding of trained sequences into the encoding of its sub-features and argues for a largely separated parallel cortical representation of movement order and timing during the production of learned sequences.

The evolution of the vertebrate and the hominoid brain from a cerebellar perspective.

Fahad Sultan

Comparative anatomy of the cerebellum has yielded important insights into its organization and function. Recent studies have focused on the output structures of the cerebellum, the deep cerebellar nuclei (DCN) and their connections with the cerebral cortex. One of these nuclei is the dentate nucleus, so called because of its heavily folded appearance in humans. The dentate nucleus is also the largest single structure linking the cerebellum to the rest of the brain. The peculiar shape and large size of the human dentate nucleus has sparked a number of theories about the role of the cerebellum in human evolution and its contribution to non-motor functions. Detailed 3D exploration of the hominoid dentate shows that the dentate complexity already emerged in the arboreal and brachiating Gibbons and Orang-Utan. In view of recent studies proposing the cerebellum to be a state-estimator or sensory predictor, I propose that this helped these early apes to occupy a special niche: arboreal life style with a frugal energy metabolism. The gibbons and the Orang-Utan predecessor maximized arboreal skills to minimize energy expenditure. In these early stages of hominoid evolution (~15Mya) the challenge on the nervous system was likely more to develop skilled low-energy-smooth upper-arm movements than social and executive prefrontal skills. In my talk, I will try to relate these findings to the special anatomy of the cerebellar microcircuitry.

It is evolutionary crucial to survive the first phase after birth. Therefore, many mammals acquire upright posture quickly. Apes and especially humans have a protracted gestational phase and in humans walking is only acquired after a lengthy arduous process. I want to argue that this is not because bipedal walking is difficult to control from the neuronal circuit's point of view. Many vertebrates show bipedal walking (e.g. the ostrich). However, in humans bipedal walking is achieved by a cerebro-cerebellar circuit. In contrast to some other circuits for motor learning

This circuit with a cognitive control of motor error.

Language and the cerebellum.

Elise Lesage and Chris Miall

University of Birmingham, School of Psychology

Even though the notion of a linguistic cerebellum remains controversial, converging evidence from clinical neuroscience, resting-state connectivity, functional MRI and studies of dyslexia implicate the cerebellum in language processing. This is apparent not just in motor functions such as articulation during speech, but also in semantic processing, such as when silently reading a sentence. However, it is unclear what the contribution of the cerebellum to these language functions is. Due to the striking cytoarchitectonic homogeneity of the cerebellar cortex, it has been suggested that cerebellar regions implicated in nonmotor processes such as language may be governed by the same computational principles as motor cerebellar regions. Hence, the cerebellar processes contributing to language may be characterised by feedforward prediction processes.

During the presentation I will present data from experiments where I have investigated cerebellar involvement in language processing using TMS and fMRI methods. A TMS experiment tested the hypothesis that the right cerebellum is involved in the short-term semantic predictions, using an eye-tracking paradigm to monitor speech processing. Results showed that participants were less able to predict the end of a spoken sentence following repetitive TMS over the right cerebellum. An imaging experiment investigated effects of a vocabulary learning task on connectivity between cerebral and cerebellar language regions, assessed in the resting state. Results confirm correlated activity between cortical language areas and the right cerebellum, and further show that functional connectivity between Broca's area and the right cerebellum increases following the acquisition of a novel vocabulary. Overall, these results further demonstrate a cerebellar role in language function and are congruent with the notion of a unified cerebellar computation, where prediction is a key element.

State Estimation in Tracking and Exploration.

M. Dagioglou & R.C. Miall

Univeristy of Birmingham, Birmingham, UK

Fast and accurate execution of movements is achieved to a large extent because the brain is able to predict their outcome. The cerebellum is believed to contain internal forward models that simulate our movements and calculate the predicted outcome. In parallel, the acquisition and selection of actions is believed to depend on the basal ganglia, which also subserve reinforcement learning. A topical issue, driven by new anatomical findings, is how these two major motor systems may interact in action acquisition.

In two recent studies we used a novel exploration task where participants were asked to find an efficient action that brings them to a hidden target. Feedback delays in the task result in the acquisition of less efficient actions, because the rewarded motor state is "hidden" by the delay. By using tDCS and a tracking task we studied if cerebellar learning can be exploited by reinforcement-based learning within the basal ganglia.

In the first study cerebellum was modulated by cathodal tDCS while participants performed the exploration task. Compared to the sham group, participants in the cerebellar group completed significantly more trials which is, partly at least, because they were able to find more efficient actions.

In a second study, we aimed to manipulate participants' performance in the exploration task by exposing them to a tracking task. Adaptation in visual feedback delays in the tracking task has been shown to be a cerebellum-based process. Participants in two groups tracked with or without delays. We hypothesized that participants would perform better in the exploration task, if they can first learn the "hidden" relationship between movements and their outcomes via the tracking task. The results suggest that tracking experience influenced the exploration performance, though not in the expected way. Participants seemed to be unable to apply their tracking experience to the exploration task, perhaps due to short exposure to tracking. However, tracking with delays lead to an increase in their proprioceptive uncertainty that changed their exploration-exploitation trade-offs in a beneficiary way.

Interplay of strategies and adaptation in motor learning.

Rich Ivry

Department of Psychology
University of California, Berkeley

Skilled performance requires facile action selection and movement execution. An expert basketball player rapidly decides whether to shoot directly to the basket or use the backboard, a decision that varies with his position on the court and the location of the defenders, and then trusts his years of practice to manipulate the ball through the net. I will review a series of studies in which we look at the interplay of strategic and implicit adaptation processes in short-term motor learning. Instructing people to use an explicit strategy to offset a visuomotor perturbation produces immediate success at the task. However, performance then deteriorates and only with extended practice, reverses to become accurate and stable. Modeling of this behavior suggests that learning entails the synergistic blending of a flexible strategy and sensorimotor adaptation processes, both of which operate continuously and in parallel. A fundamental feature of the model is that these two processes use different error signals. Whereas strategy change is driven by a goal-based error signal, adaptation is driven by a motor-based error signal. Moreover, patients with neurological disorders exhibit a double dissociation on this task: Patients with prefrontal cortex lesions fail to adjust a strategy in response to increasing performance errors, whereas patients with cerebellar degeneration show attenuated adaptation. This dissociation suggests a distributed form of control in which adaptive learning mechanisms within the cerebellum are isolated from information concerning the task goal. This lack of communication, however, may be asymmetric, an issue I will address in the second part of the talk. Here I will review studies that point to how implicit learning mechanisms associated with the cerebellum constrain the operation of goal-based processes. Understanding the interactive nature of the cerebellum and other systems involved in motor learning offers a fresh perspective to classical theories about the sequential stages of motor learning.

Posters

Cerebellar control of electronic coupling in the inferior olive I: Dendritic localization of the GABAergic nucleo-olivary terminals.

Marylka Yoe Uusisaari, Lefler Yaara and Yarom Yosef

The olivo-cerebellar loop consists of cerebellar cortex, the cerebellar nuclei and the inferior olive. The GABAergic projection from the cerebellar nuclei to the inferior olive has long been considered a critical part of the olivo-cerebellar circuitry and knowledge of its properties is critical for formulation of conceptual and computational models of the cerebellar function. Specifically, it has been proposed that the cerebellar GABAergic input to the inferior olive acts mainly via a shunting mechanism, whereby it can modify the coupling among gap-junctionally coupled IO neurons. However, regardless of the importance of this pathway in the cerebellar network, due to technical limitations this proposed functionality has not been demonstrated.

In the present two works we employ targeted expression of optogenetic tools to I) examine the anatomical organization of this pathway and II) specifically activate the GABAergic nucleo-olivary axons in a spatially constrained manner.

In the first (anatomical) part of the study, we utilize single – and double labeling of the neuronal circuit elements (NO and IO neurons) by viral transfection as well as reconstructions of individual IO neurons. This provides a three-dimensional view into the circuit structure and demonstrates that the extremely dense GABAergic innervation of the IO is mostly targeting dendritic locations. Furthermore, we explore the regional variation of the cerebello-olivary projection, prompting for further examinations of the components of this structure.

Cerebellar control of electronic coupling in the inferior olive II: Optogenetic activation of the nucleo-olivary pathway decreases coupling coefficient and eliminates sub-threshold oscillations.

Lefler Yaara, Marylka Yoe Uusisaari and Yarom Yosef

The olivo-cerebellar loop consists of cerebellar cortex, the cerebellar nuclei and the inferior olive. The GABAergic projection from the cerebellar nuclei to the inferior olive has long been considered a critical part of the olivo-cerebellar circuitry and knowledge of its properties is critical for formulation of conceptual and computational models of the cerebellar function. Specifically, it has been proposed that the cerebellar GABAergic input to the inferior olive acts mainly via a shunting mechanism, whereby it can modify the coupling among gap-junctionally coupled IO neurons. However, regardless of the importance of this pathway in the cerebellar network, due to technical limitations this proposed functionality has not been demonstrated.

In the present two works we employ targeted expression of optogenetic tools to I) examine the anatomical organization of this pathway and II) specifically activate the GABAergic nucleo-olivary axons in a spatially constrained manner.

In the physiological part of the study, we show for the first time that GABA release from nucleo-olivary terminals located on IO neuron dendrites indeed results in a reduction in electrotonic coupling as well as a blockade of the spontaneous subthreshold oscillations in the IO neurons.

DCN computation is compromised during induced strong synchrony in cerebellar Purkinje cells.

Yuval Baumel and Dana Cohen

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The neurons in the deep cerebellar nuclei (DCN) receive excitatory inputs from mossy fiber and climbing fiber collaterals and massive inhibitory input from the Purkinje cells (PC). Recent evidence in anesthetized mice shows that a major factor in determining the timing, spectral responses and firing rate of DCN neurons is the degree of synchrony in PCs converging onto a single DCN neuron (Person & Raman, 2011). We have chronically recorded neuronal activity in rat DCN to test in freely moving animals the effect of synchrony in PC activity on DCN firing patterns. Two states of PC synchrony were studied: (1) low to modest synchrony in control animals; and (2) strong synchrony elicited by systemic injection of harmaline which induces rhythmic activity in the inferior olive and cerebellar cortex. Analysis of DCN firing properties and rhythmic patterning demonstrated that in control conditions, 30% of the neurons exhibited epochs of highly defined and characteristic 7Hz rhythmic activity that did not correlate with a specific movement or with any overt stimuli. During these epochs, DCN neurons switched to bursty firing which was highly coherent between simultaneously recorded neurons. During strong PC synchrony, a higher ratio of DCN neurons (60%) exhibited rhythmic activity but with notably different spectral properties: the frequency of the rhythmic activity was broadly scattered and neuronal activity was significantly less coherent than in controls. In spite of the differences in DCN firing patterns between the two synchrony states, DCN firing rate was, on average, preserved. Our data shows that harmaline-induced high degree of PC synchrony is insufficient for generating enhanced and coherent rhythmic activity in DCN, as expected in an animal model of essential tremor, and instead compromised DCN computation.

Climbing fiber activity during trial-by-trial adaptation in the oculomotor vermis of rhesus monkeys.

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Eberhard-Karls Universität, Tübingen, Germany

The cerebellum plays a key role in motor learning, i.e. the optimization of motor behavior by considering the consequences of the behavior. It is usually assumed that information on the quality of the behavior is provided by climbing fibers, one of the two afferents reaching cerebellar cortex. Purkinje cell complex spikes (CS), the hallmark of climbing fiber activity, have been varyingly suggested to encode the motor error driving learning or, alternatively, a signal reflecting the adaptational state of the system.

In an attempt to clarify if CS encode the error driving learning, we resorted to visually guided saccades, a convenient model of goal directed motor behavior. Three Rhesus monkeys participated in the experiments, performing 10° center-out saccades in 1 out of 8 randomly chosen directions, separated by 45°. On one third of the trials, chosen at random, the visual target was stepped back by 3° during the saccade, on a second third it was stepped out by 3° or, on the final third, stayed at its initial location, thereby inducing a performance error or a regular visually guided saccade respectively. When analyzing the primary saccades, we found a tiny but nevertheless significant effect of the preceding performance error on the amplitude of the subsequent primary saccade. Its amplitude changed in a manner that would have reduced the error for this saccade if the same target shift would have taken place a second time. In an attempt to unravel the specific information, CS recorded in conjunction with the behavior might convey on the error or the changes of the behavior, we resorted to an analysis of mutual information (MI) with Bayesian binning (Endres & Földiák, IEEE Transactions, 2005). The MI analysis compared trials without error with those with errors in the one or the other directions. In ~33% of all n=129 CS subjected to this analysis, we found evidence for a significant difference between trials with errors and without. Importantly, the difference in CS activity between adapted and non adapted saccades occurred most frequently before the primary saccade, suggesting that the CS might reflect a memory trace of the error in the preceding trial. In other words, these findings support the notion that the climbing fibre offers a signature of the quality of past behavior in order to improve future manifestations of the same behavior.

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Amygdala response to an aversive stimulus is inhibited by cerebellar output.

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An aversive challenge triggers two stage learning according to the two stage theory of classical conditioning. The first stage involves a fast acquisition of fear-CRs following CS-US association in the amygdala complex. The second stage involves a slower acquisition of motor-CRs in the cerebellum. Based on the observed interaction between the cerebellum and the amygdala, being that an adaptive rate of cerebellar motor-CRs was associated with decreased amygdala-based fear-CRs, a *third stage* of classical conditioning was hypothesized. This hypothetical third stage suggests that cerebellar output has an inhibitory influence upon fear-related amygdala activity. To explore this hypothesis, we mimicked the natural cerebellar output (i.e., neuronal-CR) using electrical stimulation of the cerebellum's interpositus and fastigial nuclei, and examined how the amygdala response to an aversive periorbital electrical stimulus (i.e., mimicking the US) was influenced by the cerebellar stimulation compared to no cerebellar stimulation. The results of the study show that cerebellar output had a differential inhibitory effect upon the amygdala response to the periorbital stimulation, depending on the laterality of the cerebellar nucleus stimulated and the latency at which stimulation was triggered. These results provide a neurophysiological basis for extinction of a learned fear response by adaptive cerebellar motor responses.

Inferior Olivary signal modulation by cerebellar and extracerebellar inputs

Roni Hogri, Dor Konforty, Eyal Segalis, Matti Mintz

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One possible approach to treating localized brain tissue loss is substituting the affected brain area with a synthetic neuroprosthesis interfaced to the affected area's inputs and outputs, thus creating a closed-loop system. In the EU-based ReNaChip project, we constructed a closed-loop system composed of a biomimetic chip interfaced to the inputs and output of a cerebellar microcircuit, which successfully rehabilitated cerebellar motor-conditioning in anesthetized rats (Prueckle et al, 2011; Bamford et al, 2012). A pivotal part of designing the system was characterizing the unconditioned stimulus (US) input to the neuroprosthesis. In classical conditioning, the somatosensory US is relayed to the cerebellum by the inferior olive (IO) and is often referred to as a sensorimotor "error signal" or as a "teaching signal" driving cerebellar plasticity involved in the acquisition of conditioned responses. Moreover, cerebellar output can modulate IO activity - including firing rate and synchronicity, and IO activity can modulate cerebellar output (De Zeeuw et al., 1998; Marshall and Lang, 2009).

We examined the effects of cerebellar and extracerebellar IO inputs on the IO-US signal: i. Using a combination of *in vivo* and *in silico* methods, we demonstrated that the IO's population response to sustained periorbital airpuff-USs is shaped by an olivocerebellar negative feedback loop, interacting with intrinsically-driven subthreshold oscillations in IO neurons to transform sustained somatosensory inputs into a phasic IO output. ii. We examined the effect of cerebello-olivary inhibition on the rate and latency of conditioned motor responses in behaving rats undergoing over-learning, and suggest that this inhibition may play a role in stabilizing cerebellar plasticity. iii. Using fear conditioning in anesthetized rats, we examined the effect of emotional background on the saliency of the IO-US signal, with implications for the interactions between emotional and motor learning mechanisms (Neufeld and Mintz, 2001; Lee and Kim, 2004; Taub and Mintz, 2010).

We conclude that the IO's response to somatosensory stimuli is shaped by cerebellar and extra-cerebellar inputs, with potential implications for the acquisition and execution of conditioned motor responses. From the perspective of a closed-loop neuroprosthetic system, these olivocerebellar interactions must be taken into account in designing brain-neuroprosthesis interactions.

Firing patterns and synaptic events measured from the Deep Cerebellar nuclei

Yasmin Yarden and Yosef Yarom

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The Deep Cerebellar Nuclei (DCN) form the main output of the cerebellum. They receive inhibitory inputs from Purkinje cells (PCs) and excitatory inputs from climbing (CF) and mossy fiber (MF) collaterals. Using sharp electrode recording technique we measured intracellulary the electrical activity of DCN neurons in anesthetized mice. Neurons exhibited a variety of firing pattern ranging from low rate of irregular activity to relatively high rate bursting activity. In either case action potentials seems to be triggered by excitatory synaptic events that shift the membrane potential to its firing threshold. Spontaneous inhibitory potentials were rarely observed. Evoked responses were often observed when 500 msec air puffs were delivered to the facial area. At low puff pressure the responses are characterized by an initial large inhibitory signal followed by a barrage of excitatory events occasionally reaching the firing level. At high puff pressure, the overall spiking activity increased but the initial inhibitory response is still recognizable. It is important to note that rebound responses, where action potentials are triggered by and inhibitory events were never encountered.